General

Guideline Title

(1) Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. (2) Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. 2010 addendum. (3) Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people. 2013 addendum.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Nov. 52 p. (Technology appraisal guidance; no. 300).

National Institute for Health and Clinical Excellence (NICE). Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. 2010 addendum. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Sep. 46 p. (Technology appraisal guidance; no. 200).

National Institute for Health and Clinical Excellence (NICE). Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Aug. 31 p. (Technology appraisal guidance; no. 106).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC) and the National Institute for Health and Care Excellence (NICE): This guidance partially updates NICE TA106 'Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C' and NICE TA75 'Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C'. In September 2010, NICE released a partial review and update to NICE TA75 in order to address extensions to the marketing authorisations for peginterferon alfa-2a and peginterferon alfa-2b. Those recommendations are designated below with the label 2010 addendum. In November 2013, NICE released an addendum to NICE TA106 and TA200 to address use of peginterferon and ribavirin in children. A new and updated recommendation has been designated below with the label 2013 addendum.

- Combination therapy, comprising peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin, is recommended, within the

licensed indications of these drugs, for the treatment of mild chronic hepatitis C.

- Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C for people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated.
- The decision on whether a person with mild chronic hepatitis C should be treated immediately or should wait until the disease has reached a moderate stage ("watchful waiting") should be made by the person after fully informed consultation with the responsible clinician. The decision to treat need not depend on a liver biopsy to determine the stage of the disease if treatment is initiated immediately. However, a biopsy may be recommended by the clinician for other reasons or if a strategy of watchful waiting is chosen.
- 2010 addendum: Combination therapy with peginterferon alfa (2a or 2b) and ribavirin is recommended as a treatment option for adults with chronic hepatitis C:
    - Who have been treated previously with peginterferon alfa (2a or 2b) and ribavirin in combination, or with peginterferon alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed or
    - Who are co-infected with human immunodeficiency virus (HIV).
- 2010 addendum: Shortened courses of combination therapy with peginterferon alfa (2a or 2b) and ribavirin are recommended for the treatment of adults with chronic hepatitis C who:
    - Have a rapid virological response to treatment at week 4 that is identified by a highly sensitive test and
    - Are considered suitable for a shortened course of treatment.
- 2010 addendum: When deciding on the duration of combination therapy, clinicians should take into account the licensed indication of the chosen drug (peginterferon alfa-2a or peginterferon alfa-2b), the genotype of the hepatitis C virus, the viral load at the start of treatment and the response to treatment (as indicated by the viral load).
- There is insufficient evidence to recommend combination therapy or monotherapy with peginterferon alfa for people with mild chronic hepatitis C who have had a liver transplant.
- 2013 addendum: Peginterferon alfa in combination with ribavirin is recommended, within its marketing authorisation, as an option for treating chronic hepatitis C in children and young people.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Chronic hepatitis C

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Infectious Diseases

Internal Medicine

Pediatrics

Pharmacology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

2006 Guideline

To assess the clinical effectiveness and cost-effectiveness of pegylated and non-pegylated interferon alfa and ribavirin for the treatment of adults with histologically mild chronic hepatitis C infection

2010 Addendum

To address extensions to the marketing authorisations for peginterferon alfa-2a and peginterferon alfa-2b

2013 Addendum

To assess the clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of children and young people with chronic hepatitis C infection

Target Population

2006 Guideline and 2010 Addendum

Patients 18 years and older with mild chronic hepatitis C

2013 Addendum

Children aged 3 years and older and adolescents who have chronic hepatitis C without hepatic decompensation, who test positive for serum hepatitis C virus ribonucleic acid (HCV RNA)

Interventions and Practices Considered

1. Peginterferon alfa and ribavirin combination therapy
2. Monotherapy with peginterferon alfa
3. Decision on when to treat
4. Duration of therapy

Major Outcomes Considered

- Clinical effectiveness
    - Virological response
    - Histological improvement (e.g., inflammation/fibrosis—on biopsy)
    - Biochemical response (e.g., liver function—alanine aminotransferase)
    - Adverse effects of treatment
    - Mortality
    - Health related quality of life

- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform systematic literature reviews on the technology considered in this appraisal and prepare assessment reports. The assessment reports for this technology appraisal were prepared by the Southampton Health Technology Assessment Centre (SHTAC).

2006 Guideline

Complete methodology on the systematic literature review for NICE technology appraisal guidance 106 (TA106) 'Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C' can be found in the 2005 Assessment Report prepared by SHTAC (see the "Availability of Companion Documents" field).

2010 Addendum

In September 2010, NICE released a partial review and update to the NICE technology appraisal guidance 75 (TA75) and NICE TA106 in order to address extensions to the marketing authorisations for peginterferon alfa-2a and peginterferon alfa-2b. Complete methodology on the systematic literature review for the 2010 addendum can be found in the 2009 Assessment Report prepared by SHTAC (see the "Availability of Companion Documents" field).

2013 Addendum

The current guidance partially updates NICE TA106 'Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C' and NICE TA75 'Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C'. Complete methodology on the systematic literature review for the 2013 addendum can be found in the 2013 Assessment Report (see the "Availability of Companion Documents" field).

Clinical Effectiveness and Cost-Effectiveness

Identification of Studies for the Systematic Reviews of Clinical and Cost-Effectiveness

A search strategy was developed and refined by an experienced information specialist to identify all relevant studies investigating the two forms of peginterferon alfa with ribavirin in children and young people with chronic hepatitis C virus (HCV). Separate searches were conducted to identify studies of clinical effectiveness, cost-effectiveness, resource use/costs, health-related quality of life (HRQoL) and epidemiology. The search strategies are provided in Appendix 2 of the 2013 assessment report (see the "Availability of Companion Documents" field). Searches for clinical effectiveness and cost-effectiveness literature were undertaken from database inception to November 2012. The searches were not restricted by study design or language. The strategies were applied to the following databases:

- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Centre for Reviews and Dissemination (CRD) (University of York) databases: Database of Abstracts of Reviews of Effects (DARE), the National Health Service Economic Evaluation Database (NHS EED), and the Health Technology Assessment (HTA) database
- Medline (Ovid)

- EMBASE (Ovid)
- PreMedline In-Process and Other Non-Indexed Citations (Ovid)
- Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) and Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge)
- Biosis Previews (ISI Web of Knowledge)

Bibliographies of retrieved papers were screened for relevant studies. The manufacturers' submissions (MS) to NICE were assessed for any additional studies. Members of the advisory group who were contacted for advice and peer review were also asked to identify any additional published and unpublished references. All search results were downloaded into a Reference Manager database (Thomson Reuters, New York, USA).

Other websites, including key hepatitis C websites and symposia, were also searched for completed or ongoing studies. These included: Clinical Trials.gov, Current Controlled Trials, UK Clinical Research Network Study Portfolio (UKCRN), Health Protection Agency (HPA), Food and Drug Administration (FDA), Department of Health (DoH), Zetoc, Scirus, Hepatitis C Trust, World Hepatitis Alliance, British Association for Study of the Liver (BASL), European Association for Study of the Liver (EASL), British Liver Trust, British Society of Gastroenterology (BSG), Foundation for Liver Research, American Association for Study of Liver Diseases (AASLD), Hepatitis C Scotland, Welsh Association for Gastroenterology and Endoscopy (WAGE), British Association for Liver Disease Nursing Forum (BASLNF), HIVandHepatitis.com, Cambridge Liver Symposium and the British Viral Hepatitis Group (BVHG).

Inclusion Process

Each reference identified by the clinical effectiveness search strategy was screened for potential eligibility on the basis of title, and abstract (where available), using the inclusion criteria detailed below. Screening was carried out independently by two reviewers and the full texts of potentially relevant studies were obtained for further assessment. Screening of full papers was performed in a two-stage process. Firstly, papers were screened according to the inclusion criteria for population, intervention and outcomes using an inclusion coding sheet (see Appendix 3 of the 2013 assessment report [see the "Availability of Companion Documents" field]). Papers that fulfilled these inclusion criteria were then screened on the basis of study design according to the hierarchy outlined in the 'Study design' section below. It was not anticipated that there would be much randomised controlled trial (RCT) evidence in this population group and the two-stage process allowed an assessment of the different levels of evidence available whilst ensuring that all relevant studies were captured. Full papers were screened by one reviewer and checked by a second. At each stage, any disagreement between reviewers was resolved by discussion or involvement of a third reviewer where necessary.

Titles and abstracts identified by the cost-effectiveness search strategy were assessed for potential eligibility by two reviewers independently. Studies were only considered for inclusion if they reported the results of full economic evaluations (details below). Full papers of potentially relevant studies were retrieved and assessed for inclusion by two reviewers independently.

Inclusion and Exclusion Criteria

The following criteria are those stipulated in the final scope issued by NICE.

Population

Children and young people aged 3 to 17 years (peginterferon alfa-2b), or 5 to 17 years (peginterferon alfa-2a), with chronic hepatitis C, without liver decompensation and who are positive for HCV RNA. All groups will be considered, including:

- People with human immunodeficiency virus (HIV) co-infection
- People with all grades of severity of chronic hepatitis C (mild, moderate and severe)
- People who are treatment naïve or, if appropriate, people who have been previously treated but who relapsed or did not respond.

Interventions

- Peginterferon alfa-2a in combination with ribavirin
- Peginterferon alfa-2b in combination with ribavirin

Comparators

- Best supportive care (e.g., symptomatic treatment, monitoring, treatment without any form of interferon therapy)
- The interventions will be compared with each other within their licensed indications, i.e., peginterferon alfa-2a + ribavirin versus peginterferon alfa-2b + ribavirin

Outcomes

Studies must report sustained virological response (SVR, defined as undetectable HCV RNA at least six months after treatment cessation). Studies may also include one or more of the following:

- Virological response to treatment (e.g., during treatment, end of treatment)
- Biochemical response (e.g., alanine aminotransferase [ALT])
- Liver inflammation and fibrosis
- Mortality
- Adverse effects of treatment, including effects on growth
- Health-related quality of life (HRQoL)

Study Design

- RCTs were included if available. If no RCTs of relevance were identified, non-randomised controlled trials were considered for inclusion. Studies without a control group were only considered for inclusion in the absence of any controlled studies.
- Studies published in the last five years (i.e., since 2007) as abstracts or conference presentations were only included if sufficient details were presented to allow an appraisal of the methodology and an assessment of results to be undertaken.
- For the systematic review of cost-effectiveness, studies were only included if they reported the results of full economic evaluations (cost-utility analyses, cost-effectiveness analyses [reporting cost per life year gained], cost-benefit analyses or cost-consequence analyses).
- Systematic reviews were only used as a source of references.
- Case series, case studies, narrative reviews, editorials and opinions were not included.
- Only studies published in the English language were included.

Refer to appendices 1, 2, and 3 of the 2013 assessment report (see the "Availability of Companion Documents" field) for detailed information on search strategies for the 2013 addendum.

Number of Source Documents

Clinical Effectiveness

2006 Guideline

Three trials of peginterferon alfa-2a and five trials of interferon alfa-2b that included people with chronic hepatitis C, at least 70% of whom had mild disease, were included in the Assessment Report.

2010 Addendum

Six randomised controlled trials reported in eight publications were identified, all of which reported on peginterferon alfa and ribavirin combination therapy in people eligible for shortened courses of treatment.

2013 Addendum

Seven studies (reported in 16 publications) met the inclusion criteria.

Cost-Effectiveness

2006 Guideline

A total of 316 cost-effectiveness publications were identified. Sixty-five of these were full economic evaluations. Six of these were included.

2010 Addendum

The Assessment Group identified two studies examining the cost-effectiveness of the treatment of people co-infected with hepatitis C virus and human immunodeficiency virus (HIV).

2013 Addendum

- No studies met the criteria for inclusion, however, 2 studies are summarised in the assessment report in terms of the included patient groups, and the assumptions underpinning the economic evaluation, as they provide context for the present review.

- The manufacturers submitted 2 economic models.

Health-related Quality of Life Studies

Two studies were included in the 2013 addendum.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform systematic literature reviews on the technology considered in this appraisal and prepare assessment reports. The assessment reports for this technology appraisal were prepared by the Southampton Health Technology Assessment Centre (SHTAC).

2006 Guideline

Complete methodology on the systematic literature review for NICE technology appraisal guidance 106 (TA106) 'Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C' can be found in the 2005 Assessment Report prepared by SHTAC (see the "Availability of Companion Documents" field).

2010 Addendum

In September 2010, NICE released a partial review and update to the NICE technology appraisal guidance 75 (TA75) and NICE TA106 in order to address extensions to the marketing authorisations for peginterferon alfa-2a and peginterferon alfa-2b. Complete methodology on the systematic literature review for the 2010 addendum can be found in the 2009 Assessment Report prepared by SHTAC (see the "Availability of Companion Documents" field).

2013 Addendum

The current guidance partially updates NICE TA106 'Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C' and NICE TA75 'Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C'. Complete methodology on the systematic literature review for the 2013 addendum can be found in the 2013 Assessment Report (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Data Extraction Strategy

Data from included clinical- and cost-effectiveness studies were extracted by one reviewer using a standardised and piloted data extraction form. Extracted data were checked by a second reviewer with any discrepancies resolved by discussion or recourse to a third reviewer when necessary. Full data extraction forms of all the included studies can be found in Appendices 4 and 8 of the 2013 Assessment Report (see the "Availability of Companion Documents" field).

Critical Appraisal Strategy

The quality of the clinical effectiveness studies was assessed according to criteria based on those used by the Centre for Reviews and Dissemination (CRD, University of York). The quality of the included economic evaluations was assessed using a critical appraisal checklist based upon those proposed by Drummond and colleagues and Philips and colleagues. Quality criteria of the included studies were assessed by one reviewer, and checked for agreement by a second reviewer. Any disagreements were resolved by consensus or consultation with a third reviewer if necessary.

Methods of Data Synthesis

Clinical effectiveness data were synthesised through a narrative review with tabulation of the results of included studies. Full data extraction forms of all the included studies can be found in Appendix 4 of the 2013 Assessment Report. It was not considered appropriate to combine the studies in a meta-analysis primarily due to study design and poor study quality, with the related uncertainties. There was also some heterogeneity between studies in patient characteristics (e.g., mode of hepatitis C virus [HCV] transmission, genotype mix, treatment history), all of which can have a potential impact on the virological response to treatment.

Cost-Effectiveness

The economic analysis comprises a systematic review of the literature on the cost-effectiveness of peginterferon alfa and ribavirin treatment; a systematic review of studies of the health-related quality of life (HRQoL) of patients with chronic HCV; a review of the drug manufacturers' submissions to NICE; and an independent economic model and cost-effectiveness evaluation (the SHTAC model).

See section 5 of the 2013 Assessment Report (see the "Availability of Companion Documents" field) for additional information on cost-effectiveness analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

2006 Guideline

The Assessment Group found six studies examining the cost-effectiveness of treatment for people with mild disease. Three of these studies compared interferon combination therapy with no treatment rather than with delayed treatment. These three studies showed that interferon combination therapy was cost-effective when compared with standard care (all estimated mean incremental cost-effectiveness ratios [ICERs] were less than £10,000 per quality-adjusted life year [QALY]). Two studies compared early treatment with peginterferon alfa combination therapy with delayed treatment. They showed that, for genotypes 2 and 3, early treatment is apparently cost-effective when compared with delayed treatment, but the case for early treatment for genotype 1 is less clear.

See section 4.2 in the original 2006 guideline document (see the "Guideline Availability" field) for a detailed discussion of the cost-effectiveness evidence and interpretation, including information about non-1 genotype hepatitis C virus (HCV), genotype 1 HCV, monotherapy: all genotypes, and the sensitivity analyses.

2010 Addendum

Cost-effectiveness analyses indicate that adopting a shortened duration of treatment with peginterferon alfa-2a plus ribavirin for people with HCV genotype 1 is associated with fewer QALYs, but also with lower treatment costs, resulting in ICERs ranging from £34,000 to £65,000 of savings per QALY lost. For people with genotypes 2 and 3, a shortened treatment course with peginterferon alfa-2a plus ribavirin dominates the standard treatment duration. Similarly, for people with HCV genotype 1, a shortened duration of treatment with peginterferon alfa-2b plus ribavirin dominates the standard treatment duration. The results submitted by the manufacturers and those reported by the Assessment Group also indicate that treatment with peginterferon alfa plus ribavirin for people who are eligible for re-treatment following previous non-response or relapse of their condition is associated with QALY gains and an increase in costs. If an early stopping rule was applied at 12 weeks, re-treatment with peginterferon alfa plus ribavirin was associated with ICERs below £10,000 per QALY gained for people with HCV genotypes 1 and 4. For people with HCV genotypes 2 and 3, re-treatment was associated with ICERs below £2294 per QALY gained or dominated best supportive care. For people co-infected with HCV and HIV who were treated with peginterferon alfa plus ribavirin, either all ICERs were below £12,000 per QALY gained or treatment dominated best supportive care.

See section 4.2 in the 2010 addendum document (see the "Guideline Availability" field) for a detailed description of cost-effectiveness data, including information about manufacturers' models and the Assessment Group's model.

2013 Addendum

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The Committee considered the Assessment Group's and the 2 manufacturer's economic models.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee questioned the manufacturers' decision to rely on previous utility values without validating them and the Assessment Group's decision for using Swedish and Canadian health-related quality-of-life data, considering the Committee's preference for utility values derived from UK population studies.

The Committee noted that none of the models included disutility associated with growth impairment.

Although each of the models presented incorporated different stopping rules, the Committee would have expected the stopping rules to be consistent with clinical practice and the marketing authorisation of both products.

Spontaneous sustained virological response without treatment was not included in the manufacturers' or the Assessment Group's base-case, although they considered it in sensitivity analyses.

Nevertheless, the Committee was certain that addressing the shortcomings identified in the economic evaluations would not alter its conclusion.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values

Utility values used in the manufacturers' models were based on previous technology appraisals in adults and the values had not been updated, revalidated or presented to the Committee.

Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

Successful treatment could reduce HCV transmission rates to uninfected people in the UK population and if this benefit was included in the model, the results would likely be even more favourable.

Treatment with peginterferon alfa plus ribavirin might, in part, alleviate a mother's burden of psychological guilt of mother-to-child transmission of hepatitis C and remove concerns about horizontal transmission.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost-Effective?

Not applicable

What Are the Key Drivers of Cost-Effectiveness?

For the comparison of peginterferon alfa-2a with peginterferon alfa-2b, the key drivers of cost-effectiveness were the estimates of clinical effectiveness.

Most Likely Cost-Effectiveness Estimate (given as an ICER)

The manufacturer's and Assessment Group's base-case results showed that peginterferon alfa-2a and peginterferon alfa-2b (both plus ribavirin) dominated best supportive care in all genotypes, except Roche's cost-effectiveness results for children and young people with HCV genotype 1, 4 or 5, which resulted in an ICER of £3900 per QALY gained.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence in formulating the recommendations. Clinical effectiveness was based primarily on evidence from single-arm, uncontrolled cohort studies (only one study was randomised controlled trial). For cost-effectiveness, the manufacturers' economic models were considered.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C

Potential Harms

- Both pegylated interferon and interferon give rise to flu-like symptoms in many people.
- The most common adverse effects associated with peginterferon-based anti-viral treatments include influenza-like symptoms such as headache, fatigue, and fever, as well as insomnia, anorexia, dermatological symptoms, nausea, vomiting, and depression. The adverse effects of anti-viral treatment for hepatitis C virus, notably depression, may be more pronounced in people co-infected with human immunodeficiency virus (HIV).
- The summaries of product characteristics for peginterferon alfa-2a and -2b mention the following adverse reactions in children and young people: severe psychiatric and central nervous system effects (particularly depression, suicidal ideation and attempted suicide), weight loss and growth inhibition. The summaries of product characteristics state that, when deciding not to defer treatment until adulthood, it is important for clinicians to consider that combination therapy may inhibit growth and that it is uncertain whether this effect is reversible. Therefore the summaries of product characteristics suggest that a child or young person is treated before or after the pubertal growth spurt whenever possible.
- The most common adverse reactions to ribavirin include anaemia, dry cough and rash.

For full details of side effects and contraindications, see the Summary of Product Characteristics for each drug, available at http://emc.medicines.org.uk/ .

Contraindications

Contraindications

Peginterferon alfa-2a and -2b are contraindicated for treating chronic hepatitis C in children and young people with a history of severe psychiatric conditions.

For full details of side effects and contraindications, see the Summary of Product Characteristics for each drug, available at http://emc.medicines.org.uk/ .

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded

that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic hepatitis C and the doctor responsible for their care think that peginterferon alfa and ribavirin are the right treatments, they should be available for use, in line with NICE's recommendations.
- NICE has developed tools to help organisations put this guidance into practice (listed below) that are available on the NICE Web site (see also the "Availability of Companion Documents" field):
    - A costing statement explaining the resource impact of this guidance.

Implementation Tools

Audit Criteria/Indicators

Foreign Language Translations

Mobile Device Resources

Patient Resources

Quick Reference Guides/Physician Guides

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Nov. 52 p. (Technology appraisal guidance; no. 300).

National Institute for Health and Clinical Excellence (NICE). Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. 2010 addendum. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Sep. 46 p. (Technology appraisal guidance; no. 200).

National Institute for Health and Clinical Excellence (NICE). Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Aug. 31 p. (Technology appraisal guidance; no. 106).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Aug (addenda released 2010 Sep and 2013 Nov)

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

2006 Guideline Committee Members: Dr Jane Adam, Radiologist, St George's Hospital, London; Professor A E Ades, MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol; Dr Tom Aslan, General Practitioner, Stockwell, London; Professor David Barnett (*Chair*) Professor of Clinical Pharmacology, University of Leicester; Mrs Elizabeth Brain, Lay member; Dr Richard Cookson, Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia; Mrs Fiona Duncan, Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool; Professor Christopher Eccleston, Director, Pain Management Unit, University of Bath; Dr Paul Ewings, Statistician, Taunton & Somerset NHS Trust, Taunton; Professor Terry Feest, Professor of Clinical Nephrology, Southmead Hospital, Bristol; Professor John Geddes, Professor of Epidemiological Psychiatry, University of Oxford; Mr John Goulston, Director of Finance, Barts and the London NHS Trust; Mr Adrian Griffin, Health Outcomes Manager, Johnson & Johnson Medical; Ms Linda Hands, Consultant Surgeon, John Radcliffe Hospital, Oxford; Dr Elizabeth Haxby, Lead Clinician in Clinical Risk Management, Royal Brompton Hospital, London; Dr Rowan Hillson, Consultant Physician, Diabeticare, The Hillingdon Hospital, Uxbridge; Dr Catherine Jackson, Clinical Senior Lecturer in Primary Care Medicine, University of Dundee; Professor Richard Lilford, Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham; Dr Simon Mitchell, Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester; Ms Judith Paget, Chief Executive, Caerphilly Local Health Board; Dr Katherine Payne, Health Economist, The

North West Genetics Knowledge Park, The University of Manchester; Dr Ann Richardson, Lay representative; Professor Philip Routledge, Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff; Dr Stephen Saltissi, Consultant Cardiologist, Royal Liverpool University Hospital; Mr Mike Spencer, General Manager, Clinical Support Services, Cardiff and Vale NHS Trust; Dr Debbie Stephenson, Head of HTA Strategy, Eli Lilly and Company; Professor Andrew Stevens (*Vice Chair*) Professor of Public Health, University of Birmingham; Dr Cathryn Thomas, General Practitioner, and Associate Professor, Department of Primary Care and General Practice, University of Birmingham; Dr Norman Vetter, Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff; Professor Mary Watkins, Professor of Nursing, University of Plymouth; Dr Paul Watson, Medical Director, Essex Strategic Health Authority

2010 Addendum Committee Members: Dr Amanda Adler (*Chair*), Consultant Physician, Addenbrooke's Hospital, Cambridge; Professor Keith Abrams, Professor of Medical Statistics, University of Leicester; Dr Ray Armstrong, Consultant Rheumatologist, Southampton General Hospital; Dr Jeff Aronson, Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford; Dr Michael Boscoe, Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust; Professor John Cairns, Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine; Dr Mark Chakravarty, External Relations Director, Pharmaceuticals and Personal Health, Oral Care Europe; Professor Jack Dowie, Health Economist, London School of Hygiene and Tropical Medicine; Dr Fergus Gleeson, Consultant Radiologist, Churchill Hospital, Oxford; Ms Sally Gooch, Independent Nursing and Healthcare Consultant; Mrs Eleanor Grey, Lay member; Dr Neil Iosson, General Practitioner; Dr Rosa Legood, Lecturer, London School of Hygiene and Tropical Medicine; Mr Terence Lewis, Lay member; Dr Ruairidh Milne, Director of Strategy and Development and Director for Public Health Research, NIHR Evaluation, Trials and Studies Coordinating Centre, University of Southampton; Dr Rubin Minhas, General Practitioner and Clinical Director, BMJ Evidence Centre; Mr Stephen Palmer, Senior Research Fellow, Centre for Health Economics, University of York; Dr John Pounsford, Consultant Physician, Frenchay Hospital, Bristol; Mr Philip Pugh, Strategic Development Lead for Healthcare Associated Infection and Antimicrobial Resistance, Health Protection Agency; Dr John Rodriguez, Assistant Director of Public Health, NHS Eastern and Coastal Kent; Dr Florian Alexander Ruths, Consultant Psychiatrist and Cognitive Therapist, Maudsley Hospital, London; Mr Navin Sewak, Primary Care Pharmacist, NHS Hammersmith and Fulham; Dr Lindsay Smith, General Practitioner, East Somerset Research Consortium; Mr Roderick Smith, Finance Director, West Kent Primary Care Trust; Mr Cliff Snelling, Lay member; Professor Ken Stein (*Vice Chair*), Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter; Professor Andrew Stevens, Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham; Ms Nathalie Verin, Health Economics Manager, Boston Scientific UK and Ireland; Dr Colin Watts, Consultant Neurosurgeon, Addenbrooke's Hospital, Cambridge

2013 Addendum Committee Members: Dr Amanda Adler (*Chair*), Consultant Physician, Addenbrooke's Hospital; Dr Ray Armstrong, Consultant Rheumatologist, Southampton General Hospital; Dr Jeff Aronson, Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford; Professor John Cairns, Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine; Professor Peter Crome, Consultant Geriatrician and Professor of Geriatric Medicine; Dr Neil Iosson, General Practitioner; Anne Joshua, Associate Director of Pharmacy, NHS Direct; Dr Rebecca Kearney, Clinical Lecturer, University of Warwick; Terence Lewis, Lay Member; Dr Miriam McCarthy, Consultant, Public Health, Public Health Agency; Dr Elizabeth Murray, Reader in Primary Care, University College London; Professor Stephen Palmer, Professor of Health Economics, Centre for Health Economics, University of York; Dr Sanjeev Patel, Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital; Dr Danielle Preedy, Lay Member; Dr John Rodriguez, Assistant Director of Public Health, NHS Eastern and Coastal Kent; Alun Roebuck, Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust; Roderick Smith, Chief Finance Officer, Coastal West Sussex Clinical Commissioning Group; Cliff Snelling, Lay Member; Marta Soares, Research Fellow, Centre for Health Economics, University of York; Professor Andrew Stevens, Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham; David Thomson, Lay Member; Dr Nicky Welton, Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: The 2006 guideline and the 2010 and 2013 addenda are available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. Costing template and report. London (UK): National Institute for Health and Care Excellence (NICE); 2006 Aug. (Technology appraisal 106). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C—a systematic review and economic evaluation. Assessment report. Southampton (UK): Southampton Health Technology Assessments Centre; 2005 Oct. 251 p. Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site .
- Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (part review of technology appraisal guidance 75 and 106). Audit support. London (UK): National Institute for Health and Care Excellence (NICE); 2010. 6 p. (Technology appraisal 200). Electronic copies: Available from the NICE Web site .
- Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (part review of technology appraisal guidance 75 and 106). Costing template. London (UK): National Institute for Health and Care Excellence (NICE); 2010. (Technology appraisal 200). Electronic copies: Available from the NICE Web site .
- Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. Assessment report. Southampton (UK): Southampton Health Technology Assessments Centre; 2009 Dec. 246 p. Electronic copies: Available in PDF from the NICE Web site .
- Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people. Costing statement. National Institute for Health and Care Excellence (NICE); 2013. 4 p. (Technology appraisal 300). Electronic copies: Available from the NICE Web site .
- Hartwell D, Cooper K, Frampton G, Baxter L, Loveman E. The clinical and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people. Health technology assessment. Southampton (UK): Southampton Health Technology Assessments Centre; 2013. 215 p. Electronic copies: Available in PDF from the NICE Web site .

Additionally, audit criteria can be found in Appendix C of the 2006 original guideline document .

Patient Resources

The following are available:

- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Aug. 4 p. (Technology appraisal 106). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site . Also available in Welsh from the NICE Web site .
- Peginterferon alfa and ribavirin for chronic hepatitis C. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Sep. 4 p. (Technology appraisal 200). Electronic copies: Available in PDF from the NICE Web site . Also available in Welsh from the NICE Web site .
- Peginterferon alfa and ribavirin for chronic hepatitis C in children and young people. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Nov. (Technology appraisal 300). Electronic copies: Available from the NICE Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical

questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on February 23, 2007. This NGC summary was updated by ECRI Institute on May 5, 2011 and on February 12, 2014.

The National Institute for Health and Care Excellence (NICE) has granted the National Guideline Clearinghouse (NGC) permission to include summaries of their Technology Appraisal guidance with the intention of disseminating and facilitating the implementation of that guidance. NICE has not verified this content to confirm that it accurately reflects the original NICE guidance and therefore no guarantees are given by NICE in this regard. All NICE technology appraisal guidance is prepared in relation to the National Health Service in England and Wales. NICE has not been involved in the development or adaptation of NICE guidance for use in any other country. The full versions of all NICE guidance can be found at www.nice.org.uk .

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.